

Rolf Håkansson

Studies on Optically Active 3,3'-Bithienyls
with Special Reference to Absolute Configurations,
Conformations and Circular Dichroism Spectra

Lund 1974

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The present review summarizes results which have been obtained in connection with investigations of optically active 3,3'-bithienyls, prepared with the intention of studying the connections between the configurations and/or conformations of these compounds and their circular dichroism (CD) spectra. Two theses will be based on this material; the present dissertation is considered to include the following papers:

1. Rolf Håkansson, A useful method for structure determination of symmetrically substituted 3,3'-bithienyls.
Acta Chem. Scand. 1969, 23, 952-956.
2. Rolf Håkansson and Erik Wiklund, A useful method for structure determination of 3,3'-bithienyls by PMR. II.
Acta Chem. Scand. 1970, 24, 2667-2669.
3. Rolf Håkansson and Erik Wiklund, Stereochemistry of 3,3'-Bithienyls. I. Preparation of optically active 2,2',4,4'-tetrabromo-5,5'-dicarboxy-3,3'-bithienyl and 2,2',4,4'-tetrabromo-3,3'-bithienyl.
Arkiv Kemi 1969, 31, 101-110.
4. Rolf Håkansson, Stereochemistry of 3,3'-Bithienyls. III. On a difference between ethyllithium and butyllithium in reaction with dibromo-3,3'-bithienyls. Preparation of 3,3'-bithienylmonocarboxylic acids.
Acta Chem. Scand. 1971, 25, 1313-1326.
5. Rolf Håkansson and Erik Wiklund, Stereochemistry of 3,3'-Bithienyls. IV. On the absolute configuration of 2,2',4,4'-tetrabromo-3,3'-bithienyl and 4,4'-dibromo-2,2'-dicarboxy-3,3'-bithienyl.
Acta Chem. Scand. 1971, 25, 2109-2117.
6. Rolf Håkansson, Anders Ask and Anders Almqvist, Stereochemistry of 3,3'-Bithienyls. V. On the absolute configuration and the conformation of 4,4'-dibromo-2,2'-dicarboxy-5,5'-dimethyl-3,3'-bithienyl. Bridged 3,3'-bithienyls.
Chemica Scripta 1972, 2, 72-78.

7. Rolf Håkansson, Stereochemistry of 3,3'-Bithienyls. VI.
A new mechanism of racemization for 2,2'- and 4,4'-dilithium-3,3'-bithienyls.
Chemica Scripta 1972, 2, 109-112.
8. Rolf Håkansson, Stereochemistry of 3,3'-Bithienyls. VII.
Resolution, absolute configuration and racemization of 2,2'-dicarboxy-4,4',5,5'-tetramethyl-3,3'-bithienyl.
Chemica Scripta 1973, 3, 177-182.
9. Rolf Håkansson, Stereochemistry of 3,3'-Bithienyls. VIII.
Analysis of the circular dichroism spectra of some 2,2'-dicarboxy-3,3'-bithienyls.
Chemica Scripta 1973, 3, 212-219.
10. Erik Wiklund and Rolf Håkansson, Stereochemistry of 3,3'-Bithienyls. X. Constitution and methyl chemical shifts of 3,3'-bithienyls.
Chemica Scripta 1973, 3, 226-228.
11. Erik Wiklund and Rolf Håkansson, Stereochemistry of 3,3'-Bithienyls. XIV. On the barrier to inversion in some 3,3'-bithienyl-2,2'- and 4,4'-dicarboxylic acids and related oxepins and lactones.
Chemica Scripta in press.
12. Rolf Håkansson and Erik Wiklund, Stereochemistry of 3,3'-Bithienyls. XV. Circular dichroism of 2,2',4,4'-tetrabromo- and 2,2',4,4'-tetramethyl-5,5'-dicarboxy-3,3'-bithienyl and some related non-carboxylic open and bridged compounds.
Chemica Scripta in press.
13. Rolf Håkansson, Salo Gronowitz, Jan Skramstad and Torbjörn Frejd, Stereochemistry of 3,3'-Bithienyls. XVI. The absolute configurations, conformations and circular dichroism spectra of 4,4'-dicarboxy-2,2',5,5'-tetramethyl-3,3'-bithienyl, 4,4'-dicarboxy-2,2',5,5'-tetramethyl-3,3'-biselenienyl, 3,3',6,6'-tetramethyl-2,2'-diphenic acid and some related compounds.
Chemica Scripta in press.

14. Rolf Håkansson and Erik Wiklund, Stereochemistry of 3,3'-Bithienyls. XVII. Circular dichroism spectra of some 3,3'-bithienyl-2,2'- and -4,4'-dicarboxylic acids and corresponding mono- and bis(hydroxymethyl) and bis(bromomethyl) compounds.

Chemica Scripta in press.

15. Rolf Håkansson and Arne Svensson, Stereochemistry of 3,3'-Bithienyls. XVIII. Syntheses, absolute configurations and circular dichroism spectra of 4,4'-dicarboxy-2,2'-diformyl-3,3'-bithienyl and 2,2',4,4'-tetracarboxy-3,3'-bithienyl.

Chemica Scripta in press.

In the following these papers will be referred to as (1)...(15).

Parts IX and XI-XIII in the series Stereochemistry of 3,3'-Bithienyls, referred to as Refs. ¹⁻⁴ below and included in the thesis of my co-worker Erik Wiklund, ⁵ deal with the syntheses and the determinations of the absolute configurations of some bromo and methyl substituted optically active 3,3'-bithienyl-2,2'- and 4,4'-dicarboxylic acids, as well as of corresponding 2(4)-carboxy-2'(4')-hydroxymethyl-3,3'-bithienyls and "open" and bridged derivatives of these compounds. The CD spectra of the optically active 3,3'-bithienyls presented in Refs. ¹⁻⁴ are discussed in Papers (12) and (14). This discussion presupposes for example that the absolute configurations of the compounds are known, which means that the validity of conclusions drawn from the CD spectra may rest on the reliabilities of configurational assignments. The methods used in these connections are described below.



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1. INTRODUCTION

1.1 Atropisomerism. Previous work on biphenyl stereochemistry

Since excellent reviews and summarizing papers, covering the detailed history of biaryl stereochemistry, are available,⁶⁻¹⁶ only a brief survey of previous work in this field will be given here to place the present investigation in context.

In the beginning of the nineteen-twenties Christie and Kenner¹⁷ resolved 6,6'-dinitro-2,2'-diphenic acid (I) into optically active forms and thereby discovered the special kind of optical isomerism, which is sometimes named atropisomerism. This arises from the restricted rotation around the bond between



I

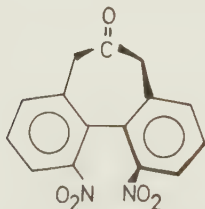
the aromatic rings, the pivot bond, due to the presence of bulky substituents at the positions ortho to this torsion axis. Atropisomerism may be found also in other types of molecules with restricted rotation around a single bond.^{7,8}

Under certain conditions this hindrance to rotation permits the isolation of optically active isomers - enantiomers. Biaryls are chiral in all conformations, attainable by rotating one aromatic ring relative to the other, except for the coplanar and in some cases the orthogonal conformations. In the latter case the molecules are chiral if the plane of one ring is not a symmetry plane for the other ring when they are at right angles to each other. If each ring is not symmetric in the way just described, in itself as in 3,3'-bithienyls or by

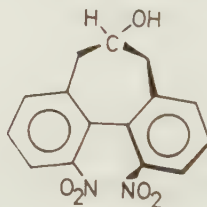
substitution as in some biphenyls, enantiomers can be inter-converted only by passing a coplanar conformation, i.e. a steric energy barrier, which can be raised by placing suitable interacting substituents at the ortho positions.

Much experimental work was carried out during the twenty years following the first resolution of I to make clear the nature of the barrier to racemization in biphenyls and the influence on the optical stability of various substituents at the ortho positions or adjacent to substituents at these positions (buttressing effects), and also at the positions para to the pivot bond. A greater understanding of the racemization mechanism and the factors of importance for the height of the energy barrier to configurational inversion was later achieved through the work of Westheimer and co-workers,⁹ Howlett¹⁸ and Pedersen.¹⁹

At the end of the fifties new interest in the field of biaryl chemistry was achieved through the important work of Mislow and co-workers. The absolute configuration of a key substance in the biaryl series, namely the biphenyl ketone II,



(R)-(-)-II



(R)-(-)-III

which can be obtained in optically active form from active dinitrodiphenic acid I, was deduced from the result of an asymmetric Meerwein-Ponndorf-Verley reduction of racemic II with (S)-(+)-2-octanol.¹¹ It was found that one enantiomer of II was reduced faster than the other to the corresponding alcohol III, and it could be concluded from molecular models that this was the (R)-form. Since the product was laevorotatory and the residual ketone was dextrorotatory, the laevorotatory form of II has the (R)-configuration, as has dextrorotatory I from which that form can also be obtained. The absolute confi-

gurations of members of the binaphthyl and biphenyl series have recently been unequivocally determined by Bijvoet X-ray analyses,²⁰⁻²² which have confirmed the absolute configurations based on the reduction mentioned above and a similar one of a binaphthyl ketone.¹¹

It was also shown that the Fredga quasi-racemate method²³ could be applied to steric correlations of biphenyls, and in this and various other ways the absolute configurations of a great many biphenyl derivatives could be deduced.¹¹

Shortly before the establishment of absolute configurations of biaryls, instruments for measuring optical rotatory dispersion (ORD) had become commercially available, and Djerassi had initiated his excellent ORD studies of the keto chromophore.²⁴ In the beginning of the sixties Mislow and co-workers investigated the ORD spectra of a great many biphenyls and binaphthyls, unbridged (open) and singly bridged,¹³ and some doubly bridged biphenyls as well.¹⁴ The ORD measurements were complemented by circular dichroism (CD) investigations.^{15,16}

The instruments used at that time permitted penetration to about 220 nm under ideal conditions, but often only to 240-250 nm. However, this was sufficient for reaching an important Cotton effect situated at 240-250 nm in the spectra of most compounds and associated with an absorption band referred to as the conjugation band. It was shown that the position of this band and the magnitude of the corresponding Cotton effect reflected the size of the torsional angle between the ring planes (a blue shift for increasing angles), and it was suggested that the sign of this Cotton effect reflected the helicity of the biaryl skeleton. An (M_x)-helicity, which means a cis-skew conformation of the (R)-biaryl, would result in a positive effect at 240-250 nm (Fig. 1).

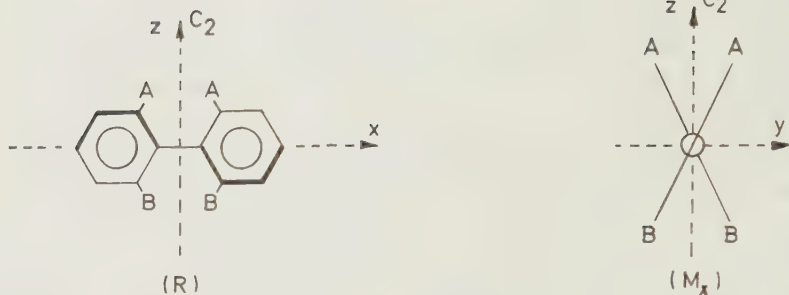
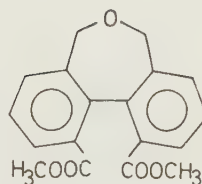


Figure 1. Illustration of the helicity of a biphenyl.

(M_x) means that the near ring should be rotated in the negative direction (minus) to cover the far ring (smallest angle) if the molecule is viewed along the x-axis, which is the long-axis of the molecule. Part of a left-handed helix can be seen. If the molecule is viewed along the z-axis (C_2 -axis) part of a right-handed helix may be visualized and the symbol is then (P_z) (plus) in the example given. For the trans-skew conformation the symbols will be (P_x) and unchanged (P_z).

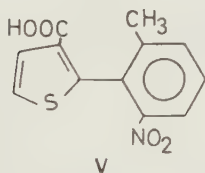
Cotton effects were also observed at longer wavelengths and rules were given for the connections between the absolute configurations of various types of compounds and the signs of these effects in the ORD and CD spectra. For example, it was stated¹³⁻¹⁶ that for the conformationally rigid 2,2'-bridged biaryls of (R)-configuration the sign of the long wavelength Cotton effect is negative for 6,6'-dinitro derivatives, positive for 6,6'-dimethyl and 6,6'-dichloro derivatives and positive for 1,1-binaphthyls. Opposite signs in the spectra of corresponding open compounds might indicate another helicity of their biaryl skeletons,¹³ but it was also found that flexible substituents influenced the spectra. In the ORD spectrum of the bridged (R)-diphenic acid dimethyl ester IV the sign of an intense Cotton effect near 260 nm, probably corresponding to the conjugation band effect mentioned above, was opposite to that expected. The conclusion was drawn that the twist of the

ester groups relative to the rings might constitute an inherently chiral chromophore, giving rise to a special Cotton effect which reflects that twist.¹⁴

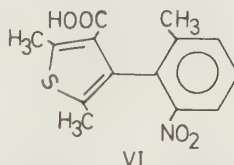


IV

1.2 Previous work on bithienyl stereochemistry



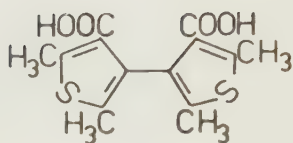
V



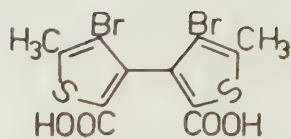
VI

The first examples of demonstrated atropisomerism in thiophene compounds are shown in formulas V och VI. Compound V, which is optically unstable at room temperature, was resolved by Owen and Nord²⁵ in 1951 and VI was later resolved by Jean, Owen and Nord.²⁶ The latter authors also prepared bithienyl VII and they concluded from its UV spectrum that it was probably resolvable. Gronowitz and Beselin²⁷ later performed the resolution of VII, prepared through a new synthetic path.

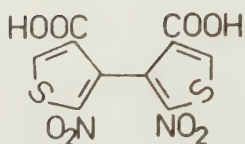
Atropisomerism in the 3,3'-bithienyl series, however, was first demonstrated by Gronowitz and Frostling²⁸ in 1961 through the resolution of 4,4'-dibromo-2,2'-dicarboxy-5,5'-dimethyl-3,3'-bithienyl (VIII) into its enantiomers. Nitro compounds IX and X were prepared by Gronowitz and Gustafson²⁹ and Gronowitz and Dahlgren,³⁰ respectively. The absolute configurations of IX²⁹ and X³¹ were established by the Fredga quasi-racemate method. The dextrorotatory forms have the (R)-configuration. The CD spectra of IX and X and the corresponding dimethyl esters were discussed by Gronowitz.³¹ Gronowitz and Skramstad³² made a racemization study of VII and XI in 0.1 N sodium hydroxide (cf. Paper 11). The biphenyl analogue XII³³ could not be



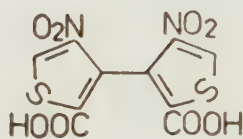
VII



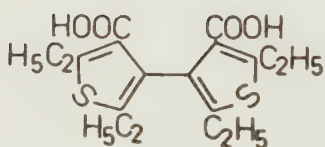
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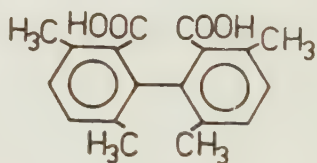
IX



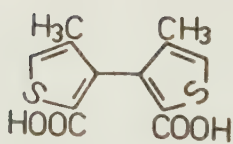
X



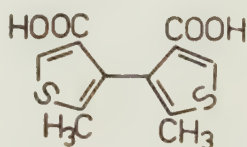
XI



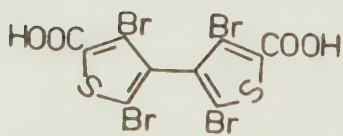
XII



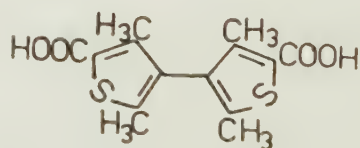
XIII



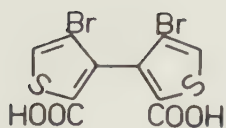
XIV



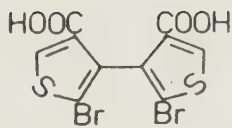
XV



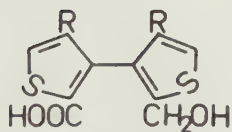
XVI



XVII

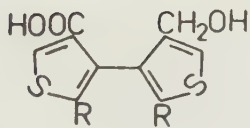


XVIII



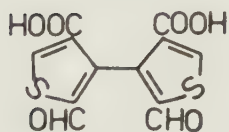
XIX R=Br

XX R=CH₃

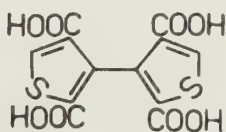


XXI R=Br

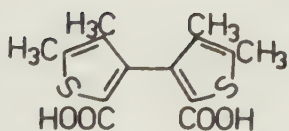
XXII R=CH₃



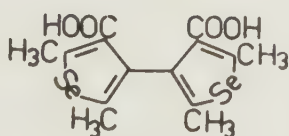
XXIII



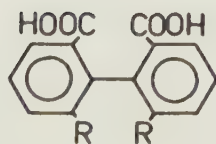
XXIV



XXV

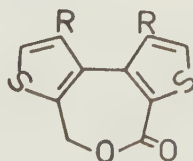


XXVI

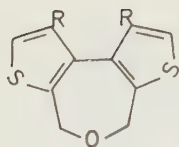


XXVII R=CH₃

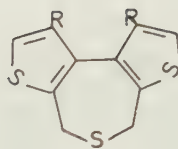
XXVIII R=Cl



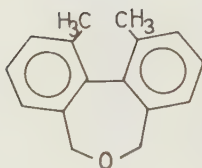
XXIX



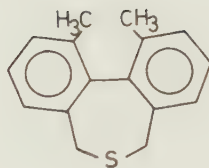
XXX



XXXI



XXXII



XXXIII

measurably racemized in the same solvent at 150°C for four hours. The racemic forms of methyl compounds XIII and XIV were prepared by Gronowitz and Hagen.³⁴

Attempts to resolve 5-carboxy-3,3'-diiodo-2,2'-bithienyl,³⁵ 5,5'-dicarboxy-3,3',4,4'-tetraiodo-2,2'-bithienyl³⁶ and 5,5'-dicarboxy-4,4'-diiodo-3,3'-bithienyl³⁶ failed, probably due to the expected low steric barrier to rotation in these compounds.

The present work was initiated by Professor Salo Gronowitz and it constitutes a direct continuation of the previous investigations of 3,3'-bithienyls mentioned.

2. SYNTHESSES OF 3,3'-BITHIENYLS

The bithienyls investigated have all been considered as derivatives of 3,3'-bithienyl although in some cases the name 4,4'-bithienyl might have been more correct. With the nomenclature selected a convenient division into for example 2,2'-, 4,4'- and 5,5'-dicarboxylic acids is possible, which has been of great advantage in for instance discussing ^1H -NMR shifts of methyl esters and not least CD spectra.

The systems investigated in CD are represented in formulas VII-XXVIII by the resolvable parent compounds and include the dicarboxylic acids VII-XIV, prepared by Gronowitz and co-workers as mentioned above, carboxylic acid XXV, synthesized by Wiersema and Gronowitz in other connections,³⁷ and bisele-nienyl XXVI, prepared by Gronowitz and Frejd.³⁸ Biphenyls XXVII-XXVIII and XXXII-XXXIII, also investigated, were generous gifts from Professor Kurt Mislow. Compounds XIII and XIV were prepared through an alternative synthetic path⁴ (see below).

Before 1960, 2,2'- and 3,3'-bithienyls and their derivatives were difficultly attainable and considered more or less as laboratory curiosities. Only a few derivatives were known.³⁹ The syntheses involved Ullmann coupling between thienyl halogenides, giving low yields of bithienyls. In 1961 Gronowitz and Karlsson⁴⁰ reported that 2- and 3-thienyllithium, easily available from 2- and 3-bromothiophene, respectively,⁴¹ and cupric chloride gave relatively good yields of 2,2'- and 3,3'-bithienyls, and thereby a synthetic path to compounds of this kind was opened.

Substituents such as methyl groups, which do not interact with organolithium compounds, can be introduced in the thiophene ring before coupling. In this way the bithienyl skeletons of compounds VII,²⁷ VIII,²⁸ XI,³² XIII³⁴ (cf. below), XIV³⁴ (cf. below), XVI¹ and XXV³⁷ were prepared. In VIII, XIII, XVI and XXV, the carboxyl groups were introduced by metallation of the coupling products at the α -positions with alkyllithium and

subsequent carbonation. In the case of XIII, metallation occurred at both 2,2'- and 5,5'-positions.³⁴

The reactions of 3,3'-bithienyl are similar to those of thiophene (3-substituted). The effect of a thienyl group as substituent at the 3-position may be revealed from the fact that 3,3'-bithienyl is brominated in the 2,2'-positions by N-bromosuccinimide.⁴² The product decomposes relatively easily⁴² (cf. Paper 4). To place substituents at the 4,4'-positions, the four α -positions must usually be blocked. For example, to obtain XIV, Gronowitz and Hagen³⁴ iodinated 2,2'-dimethyl-3,3'-bithienyl with iodine-iodic acid^{43,44} to 4,4',5,5'-tetraiodo-2,2'-dimethyl-3,3'-bithienyl. The 5,5'-iodines were removed after halogen-metal exchange with alkyl-lithium, followed by hydrolysis of the resulting 5,5'-dilithium derivative. Subsequent halogen-metal exchange at the 4,4'-positions, followed by carbonation of the dilithium intermediate, yielded XIV.

The 4,4'-substituents in nitro compounds IX were introduced in the following way²⁹: 3,4-dibromothiophene was coupled via the 3-lithium derivative to yield 4,4'-dibromo-3,3'-bithienyl.⁴⁵ After halogen-metal exchange with alkyllithium and subsequent carbonation, 4,4'-dicarboxy-3,3'-bithienyl⁴⁵ was obtained. This carboxylic acid was nitrated at the 2,2'-positions to yield IX.²⁹

In connection with the preparation of XVIII³ and XXIV (15) attempts were made to brominate and to iodinate 4,4'-dicarboxy-3,3'-bithienyl, which resulted in mixtures of products with halogen atoms at the 2,2'- and 5,5'-positions. Compound XVIII was instead prepared³ by bromination of 4,4'-diformyl-3,3'-bithienyl in the presence of aluminium trichloride, which is known to strongly enhance the meta directing property of the formyl group.^{46,47} Oxidation of the product gave XVIII³ and in an intramolecular Cannizzaro reaction the dialdehyde afforded hydroxy acid XXI.³ Hydroxy acids XIX,² XX and XXII⁴ were prepared in similar reactions from the appropriate diformyl compounds.

The examples above may have indicated some synthetic methods available for the preparation of 3,3'-bithienyls and the problems involved.

2,4-Dibromothiophene is a very useful starting material for the preparation of 2,4-disubstituted thiophenes.⁴¹ After halogen-metal exchange with alkyllithium at -70°C , suitable substituents may be introduced at the 2-positions by reacting the intermediate 4-bromo-2-lithium intermediate with various reagents. The reaction may then be repeated at the 4-positions if the 2-substituent in itself (or after suitable protection) does not react with organolithium compounds.

To obtain resolvable 3,3'-bithienyls, the 2,2'- and 4,4'-positions must be substituted (at least three of the four positions). 2,2',4,4'-Tetrabromo-3,3'-bithienyl was considered to be very useful for the syntheses of 2,2',4,4'-tetrasubstituted 3,3'-bithienyls in reaction sequences similar to those starting from 2,4-dibromothiophene described above.

The preparation of 2,2',4,4'-tetrabromo-3,3'-bithienyl is presented in Paper (3), and a useful modification is reported in Ref.². Hexabromo-3,3'-bithienyl, easily obtainable from 3,3'-bithienyl and bromine, reacts with alkyllithium at the 5,5'-positions, and hydrolysis of the intermediate 5,5'-dilithium derivative yields the desired tetrabromo compound. Carbonation instead of hydrolysis affords dicarboxylic acid XV.

Compounds XIII,⁴ XIV,⁴ XVII (5), XIX,² XX,⁴ XXII⁴ and XXIII (15) were prepared from 2,2',4,4'-tetrabromo-3,3'-bithienyl. The corresponding 2,2'-dilithium derivative yielded XVII on carbonation, whereas reaction with dimethyl sulphate introduced the 2,2'-dimethyl groups in XIV and XXII, and reaction with N,N-dimethyl formamide gave 4,4'-dibromo-2,2'-diformyl-3,3'-bithienyl. The formyl groups were protected against organolithium compounds through acetal formation with methanol.⁴ Via the 4,4'-dilithium derivatives of the compounds first obtained, 4,4'-substituents were introduced in reactions similar to those above; in XIV and XXIII by carbonation, in XIII and XX by reaction with dimethyl sulphate, and in XXII by reaction with N,N-dimethyl formamide. Acetals were hydrolyzed and the formyl groups transformed by oxidation or intramolecular Cannizzaro reactions to yield the desired compounds.

2,2',4,4'-Tetrabromo-3,3'-bithienyl is also available in optically active form through decarboxylation of active XV (3). Attempts to prepare optically active 3,3'-bithienyls from the

active tetrabromobithienyl via the 2,2'-dilithium derivative failed, since the latter compound racemizes (5) (see below). Via the corresponding 2-monolithium derivative, however, an active monocarboxylic acid (XXXIV in Scheme 2 below) could be prepared (5). In a similar reaction with active 4,4'-dibromo-2,2',5,5'-tetramethyl-3,3'-bithienyl, active 4-bromo-4'-carboxy-2,2',5,5'-tetramethyl-3,3'-bithienyl (XXXV, Scheme 2) was obtained, but the 4,4'-dilithium derivative racemized (6). Of course it would have been of great advantage to be able to prepare active 3,3'-bithienyls from active 2,2',4,4'-tetrabromo-3,3'-bithienyl via the dilithium derivatives.

Aldehyde XXIII could be oxidized to tetracarboxylic acid XXIV, but yields were low (15). The latter compound was also prepared (15) from 3-bromo-2,4-dicarbomethoxythiophene in an Ullmann type of reaction using N,N-dimethyl formamide as solvent.⁴⁸ In a similar reaction, Gronowitz and Dahlgren³⁰ previously prepared nitro compound X from 3-bromo-2-carbomethoxy-4-nitrothiophene. In both cases it was found that the desired reaction was difficult to repeat; often it resulted in a reduction of the halogen atoms, affording the dehalogenated thiophenes and low yields of coupled products only. The dimethyl ester of XVII was also obtained in low yields in a modified Ullmann reaction (3).

Several optically active derivatives of the compounds shown in formulas VII-XXV were prepared by transformations of the carboxylic groups or bromination in accessible positions. From the bis(hydroxymethyl) compounds obtained after reduction of the carboxylic groups, oxepins of the type shown in formula XXX and corresponding 4,4'-bridged compounds were prepared (6,8).²⁻⁴ The oxepins, however, were optically inactive, and so were the lactones of type XXIX and corresponding 4,4'-bridged compounds obtained from optically active XIX and XXI (11).^{2,3} From optically active 2,2'- and 4,4'-bis(bromomethyl) derivatives of 3,3'-bithienyls, prepared from the corresponding bis(hydroxymethyl) compounds, optically active 2,2'- and 4,4'-bridged thiepins of the type shown in formula XXXI were prepared. Examples of such reaction series are given in Papers (6) and (8) and are also found in Refs.²⁻⁴.

In several cases the bis(bromomethyl) compounds were reduced to methyl groups. It was found that carboxyl groups could also be reduced directly to methyl groups using lithium aluminium hydride-aluminium trichloride 1:4 as reagent (6,8).²⁻⁴ The same reagent in the ratio 1:1 was used for reduction of carboxylic groups to the corresponding alcohols (6,8).²⁻⁴ In the reduction of 2,2'-dicarboxylic acids some methyl compounds were formed as by-products, in particular in the case of non-halogenated compounds (8).⁴ The advantage with the reagent mentioned is that α -bromines are not reduced, as they are in the absence of aluminium trichloride, at least in thiophenes (6).³

In connection with the preparations of the monocarboxylic acid XXXIV (Scheme 2) from active 2,2',4,4'-tetrabromo-3,3'-bithienyl via the 2-lithium derivative, it was found that a large amount of the corresponding 2,2'-dicarboxylic acid was also obtained if ethyllithium (1 equiv.) was used in the reaction but not on using butyllithium (1 equiv.). Since this was of synthetic and also of theoretical interest, a closer investigation was performed, which is presented in Paper (4). In summary it was found that 2,2'-dibromo-3,3'-bithienyls with 1 equivalent of butyllithium at -70°C and subsequent carbonation gave mainly monocarboxylic acids, whereas ethyllithium yielded a mixture of mono- and dicarboxylic acids with the latter constituting at least 55-60 % of the product. 4,4'-Dibromo-3,3'-bithienyl was metallated at one of the 5-positions, and when these were blocked by methyl groups, the 2-position, in addition to the 4- and 4'-positions, was attacked by both alkyllithium compounds.

3. STRUCTURE DETERMINATIONS

In many cases the molecular structure of the 3,3'-bithienyls investigated follows from the methods of synthesis, and each step is easily followed for example by IR, ^1H -NMR and elemental analyses. The various coupling constants for thiophenes⁴¹ are valid for bithienyls as well. The structure of 2,2',4,4'-tetrasubstituted 3,3'-bithienyls often follows from their atropisomerism. Most certainly, as mentioned above, at least three of the four ortho positions must be substituted to permit enantiomers to be isolated, and a symmetric constitution of the compounds is in most cases easily deduced by ^1H -NMR analyses.

On the basis of ^1H -NMR data obtained from 3,3'-bithienyls, the structures of which could be deduced as mentioned just above, it was shown that the carbomethoxy resonances (1,2) and the methyl resonances (10) of such compounds can be used for structure determinations. In 5,5'-dicarbomethoxy-3,3'-bithienyls, the OCH_3 resonances occur within the small interval of 3.80-3.90 δ (6.10-6.20 τ) but are shifted upfield 0.2-0.3 ppm in 2,2'- and 4,4'-dicarbomethoxy-3,3'-bithienyls (1). The same is valid for the corresponding monomethyl esters as well (2). For the methyl resonances of unbridged 3,3'-bithienyls without substituents such as carboxyl or formyl groups, the following values are valid: $\delta_{4,4'-\text{CH}_3} = 1.69\text{-}2.07$ ppm; $\delta_{2,2'-\text{CH}_3} = 2.05\text{-}2.36$ ppm; $\delta_{5,5'-\text{CH}_3} = 2.28\text{-}2.43$ ppm.

The differences may appear small but nevertheless they are significant. Some overlap of the intervals occurs in the case of methyl resonances. However, as shown in Paper (10) this causes no confusion, provided that the effects of other substituents present are considered.

Bridging causes a low-field shift of the resonances of the 2-(2'-)- and 4-(4'-)-methyl groups. The same effect is produced by 4-(4'-)-carboxylic groups on the 5-(5'-)-methyl resonances and by 5-(5'-)-carboxylic groups on the 4-(4'-)-methyl resonance.

Application of the differences in the carbomethoxy resonances in 3,3'-bithienyls to structure determinations are found, for example, in Paper (4).

4. RESOLUTIONS

The compounds shown in Formulas VII-XXV (XXVI) can all be resolved by conventional methods via the mono- or disalts of optically active bases such as brucine, quinine, quinidine, cinchonine, cinchonidine and dehydroabietyl amine. Often optical purity appeared to be achieved after one or two recrystallizations of the diastereomeric salts. Active XXIII was obtained through a second-order asymmetric transformation (15). Several optically active 3,3'-bithienyls were obtained from the active carboxylic acids by transformation of the carboxyl groups, as mentioned above.

5. OPTICAL STABILITIES

The optical stabilities of 3,3'-bithienyls are lower than those of the corresponding biphenyls, which is an expected consequence of the different ring sizes in the two systems. In Paper (8) the racemization of the disodium salt of 2,2'-dicarboxy-4,4',5,5'-tetramethyl-3,3'-bithienyl (XXV) is presented and compared with that of the disodium salt of the 4,4'-dicarboxy isomer VII, studied by Gronowitz and Skramstad.³² It was found that the racemization enthalpy of the 2,2'-dicarboxylic acid is about 4 kcal/mol (1 cal = 4.18 J) higher than that of the 4,4'-dicarboxylic acid. At first this was considered to depend on a different buttressing effect of the 5,5'-methyl groups on the methyl or carboxyl groups, at the 4,4'-positions. However, comparisons with the racemization enthalpies of the disodium salts of XIII and XIV revealed that the 5,5'-dimethyl groups were of minor importance in this connection (11); 2,2'-dicarboxy-3,3'-bithienyls seem to be more optically stable than the corresponding 4,4'-dicarboxylic acids at least when methyl groups and bromines (XVII, XVIII) are the other blocking substituents (11).

To investigate if differences in the geometries at the 2,2'- and 4,4'-positions of 3,3'-bithienyl might account for the results obtained, simple calculations of the bond bending forces and van der Waals' interactions involved were performed (11) on models of VII, the corresponding biselenienyl XXVI, and compounds XXV, XIII and XIV, using a desk calculator. In the models of the 3,3'-bithienyls the 4,4'-systems were as stable as the corresponding 2,2'-systems, however. The interactions of 4-(4'-)-carboxyl and 5-(5'-)-methyl groups in the activated state were small, while those of 4-(4'-)-methyl and 5-(5'-)-methyl groups were somewhat greater with the mechanism for racemization assumed in the models.

Carboxyl groups may be difficult to treat in calculations of the kind mentioned, but by using parameters applicable to

such groups, mainly found in the work of Scheraga et al.,⁴⁹ good agreement between calculated and experimental results was obtained. (Differences in energies between the activated complexes involved were considered at first hand.)

In Paper (15) the racemizations of XXIII and XXIV are reported. Dialdehyde XXIII is easily racemized at about 50°C in diglyme; in aqueous sodium hydroxide at room temperature an intramolecular Cannizzaro reaction takes place in addition to racemization. The optical stability of the tetrasodium salt of XXIV may be compared with that of the disodium salt of VII. The acidic form of XXIV is more stable.

In Papers (6) and (8) the barriers to configurational inversion of two oxepins of type XXX, obtained from VIII and XXV, respectively, are given and a comparison with the stabilities of some related 2,2'- and 4,4'-bridged compounds of type XXX and XXIX in deuterated dimethyl sulphoxide is made in Paper (11). In the ¹H-NMR spectra of such compounds the methylene protons of the bridge, due to magnetic non-equivalence, exhibit an AB quartet. From the coalescence temperature of the quartet the rate of inversion and the associated free energy, $\Delta G_C^\ddagger$, may be calculated.⁵⁰ The 2,2'- and 4,4'-bridged compounds of types XXIX and XXX, with bromines or methyl groups as blocking substituents, are of virtually the same stabilities. $\Delta G_C^\ddagger$ values of 17-23 kcal/mol⁻¹ (1 cal = 4.18 J) were obtained, which are probably too low to permit separation into enantiomers at ordinary temperatures. For comparison it may be mentioned that the $\Delta G_{\text{rac}}^\ddagger$ value for the 6,6'-dichloro analogue of biphenyl XXXII (obtained from XXVIII) is 34.1 kcal/mol⁻¹.⁵¹

As mentioned above it was found that the 2,2'- and 4,4'-dilithium derivatives of 3,3'-bithienyl racemize very quickly even at -70°C, which means complete loss of optical activity in the carbonation products after halogen-metal exchange reaction for only a few seconds. Probably the lithium compounds lose activity directly on formation, which might be consistent with an achiral structure. On the basis of what was known about structures and bonding in alkylolithiums^{52,53} and in for example the dimer of triphenylaluminium,⁵⁴ an achiral structure was proposed for 2,2'- and 4,4'-dilithium-3,3'-bithienyls, in which the aromatic rings are coplanar and the lithium atoms form bridges between the 2,2'- or 4,4'-positions by means of electron-deficient bonds (7).

6. DETERMINATIONS OF ABSOLUTE CONFIGURATIONS

The establishments of the absolute configurations of compounds VII-XXVI, from which other optically active compounds investigated in CD were obtained, are shown in Schemes 1 and 2. (T means thermal analysis, generally of dimethyl esters; in the case of the combination XI:VII diamides and in the combination XXVI:VII the corresponding diols were analyzed. C means chemical methods, X X-ray powder photographs and CD circular dichroism spectra.)

The steric relations of nitro compounds IX and X to I^{29,31} and those of compounds XXVI and XI to carboxylic acid VII (13)³⁸ were deduced by Gronowitz and co-workers.

Bromo compound XVII was related to nitro compound X by the quasi-racemate method (5). The determinations of the absolute configurations of the compounds in the system represented by XV were more difficult, due to the equivalent substituents at the 2,2'- and 4,4'-positions. As indicated above attempts to transform active 2,2',4,4'-tetrabromo-3,3'-bithienyl to 2,2'-dicarboxylic acid XVII via the dilithium derivative failed, due to the racemization of the latter intermediate. However, decarboxylation of active XVII with mercuric acetate gave an active mercury derivative, which could be transformed into active hexabromo-3,3'-bithienyl with potassium tribromide as shown in Paper (5) (Scheme 1). Active hexabromo-3,3'-bithienyl is easily obtained from XV (5).

Some racemization occurred, however, and in a similar reaction to transform active dicarboxylic acid VIII to active 2,2',4,4'-tetrabromo-5,5'-dimethyl-3,3'-bithienyl (Scheme 1), the racemization was extensive unless the reaction was performed within about a minute (6). The active product was also obtainable from active hexabromobithienyl via the 5,5'-dilithium derivative in reaction with dimethyl sulphate (6).

In optically active biphenyls blocking ortho substituents have been exchanged, for example amino groups in Sandmeyer reactions, with retained optical activity in the products (see Ref.¹¹ and references therein).

Compounds VIII and XXV were sterically related (Scheme 1) by thermal analyses of the corresponding esters; those with the same mode of rotation formed a solid solution, indicating related configurations (8).

The absolute configuration of hexamethyl-3,3'-bithienyl, derived from active XVI by decarboxylation to active 2,2',4,4'-tetramethyl-3,3'-bithienyl and subsequent introduction of the 5,5'-dimethyl groups (Scheme 2), could be deduced by reduction of the carboxyl groups of active XXV to yield the hexamethyl compound¹ (Scheme 1). In a similar way 4,4'-dicarboxylic acid VII was sterically related to hexamethyl-3,3'-bithienyl (13) (Scheme 1). Biselenienyl XXVI was previously sterically related to VII by Gronowitz and Frejd³⁸ (Scheme 1).

The absolute configuration of 4,4'-dicarboxylic acid XVIII was established by thermal analysis of the dimethyl esters of XVIII and IX³ (Scheme 1). The CD spectra of XVIII and VII of the same assigned configuration are similar (13,14).

Compounds XIII, XIV⁴ and XXIII (15) were sterically related to 2,2',4,4'-tetramethyl-3,3'-bithienyl by reduction of the carboxy and aldehyde groups, and active XXIII was oxidized to active XXIV (15) (Scheme 2). Hydroxy acids XIX-XXII were oxidized to the corresponding dicarboxylic acids (Schemes 1 and 2).

Active monocarboxylic acids XXXIV and XXXV (Scheme 2) were obtained from active 2,2',4,4'-tetrabromo-3,3'-bithienyl (from XV) and active 4,4'-dibromo-2,2',5,5'-tetramethyl-3,3'-bithienyl, respectively, via the monolithium derivatives as mentioned above (5,6). The latter 4,4'-dibromo compound was obtained from VIII after reduction of the carboxylic groups to methyl groups.

The monocarboxylic acids mentioned, when derived from (R)-XV and (R)-VIII, should be assigned the absolute configuration symbol (S) according to existing rules.⁵⁵ Since the twist of the biaryl skeletons are the same as in other 3,3'-bithienyls of (R)-configuration, a rule for the assignment of absolute configurations in such compounds was proposed, according

to which the heteroatoms of the aromatic rings take precedence over the substituents and the symbol was suggested to be (R') (5). The CD spectra of (R')-XXXIV and (R')-XXXV are also similar to those of the (R)-forms of XIX-XX and XXI-XXII, respectively (14).

The absolute configuration of biphenyl XII was deduced from comparisons of the CD spectra of XII with those of XXVII in various solvents and the result was confirmed from a study of the X-ray powder photographs of combinations of active XII and active VII (13).

7. CIRCULAR DICHROISM SPECTRA

CD spectra of 3,3'-bithienyls are discussed mainly in Papers (9) and (12-14). Those of compounds XXIII-XXIV are presented in Paper (15). In Paper (9) the CD spectra of some 2,2'-dicarboxylic acids and those of the dimethyl ester, the diamide and the acid dichloride of XXV are analyzed. Paper (12) deals with the CD spectra of 5,5'-dicarboxylic acids XV and XVI, with those of bridged compounds and with the spectra of several bromo and methyl derivatives of 3,3'-bithienyl. The CD spectra of some 4,4'-dicarboxylic acids are discussed in Papers (13) and (14), and in the former paper the spectra of bithienyl VII is compared with those of biselenienyl XXVI and biphenyls XII and XXVII. The CD curves of hydroxy acids XIX-XXII and of 2,2'- and 4,4'-bis(hydroxymethyl) and corresponding bis(bromomethyl) compounds are presented in Paper (14).

CD investigations may be performed for various reasons. The main purpose is usually to obtain information about absolute configurations and/or conformations through comparisons with the spectra of related compounds of known stereochemistry or through the application of existing rules.⁵⁶ The purpose may also be to collect data for formulations of empirical rules for the determinations of molecular geometries from CD spectra, which has in part been the aim in the present investigations.

However, CD spectra may also offer valuable information of interest for spectroscopists and for theoreticians, who are working with the problems of the mechanism of optical activity in various systems. To increase interest in these fields in the case of bithienyls and of biaryls in general, extensive investigations of several CD spectra have been carried out.

7.1 Absolute configurations from CD spectra

The absolute configurations of various classes of 3,3'-bithienyls are reflected in their CD spectra, as is the case for biphenyls.¹³⁻¹⁶ In the UV spectra of 3,3'-bithienyls three main absorption bands may be observed; one band above 250 nm, most evident in the spectra of 2,2'-dicarboxylic acids, one band near 250 nm and a third one near 200 nm. Often the long wavelength band appears to nearly coincide with the 250 nm band (Figs. 2-4).

The most characteristic feature in the CD spectra of 3,3'-bithienyls of (R)-configuration is the presence of a negative band near or above 250 nm followed by a positive band at shorter wavelengths. Both bands appear to be associated with the 250 nm absorption band. In Figs. 2-4 some examples are given.

Exceptions to this rule among the compounds investigated are those with flexible substituents such as carboxylic groups (13,14), bromomethyl groups (14) and eventually nitro groups (13) at the 4,4'-positions. The nitro compounds are currently under investigation. The characteristic pattern mentioned is observed for example in the spectra of 3,3'-bithienyls with carboxylic groups at the 2,2'- or 5,5'-positions (9, 12, 14) (Fig. 2), with bromines or methyl groups at the 2,2'- and 4,4'-positions (12) (Fig. 3), with hydroxymethyl or bromomethyl groups at the 2,2'-positions (14), with hydroxymethyl groups at the 4,4'-positions (14), and in the spectra of 2,2'- and 4,4'-bridged 3,3'-bithienyls (12) (Fig. 4). In the cases of 2,2'-dicarboxylic acids (Fig. 2) and the bridged compounds (Fig. 4) the intensities of the 250 nm effects are relatively high; the ellipticity values are of the order of 10^5 (Figs. 2, 4).

Derivatives of 2,2'-dicarboxylic acids, such as dimethyl esters, amides and acid chlorides appear to exhibit spectra similar to those of the parent compounds, as do the disalts of the acids mentioned (9, 14)³¹ (Fig. 2). The spectra of these compounds are influenced by solvent changes only to a minor extent.

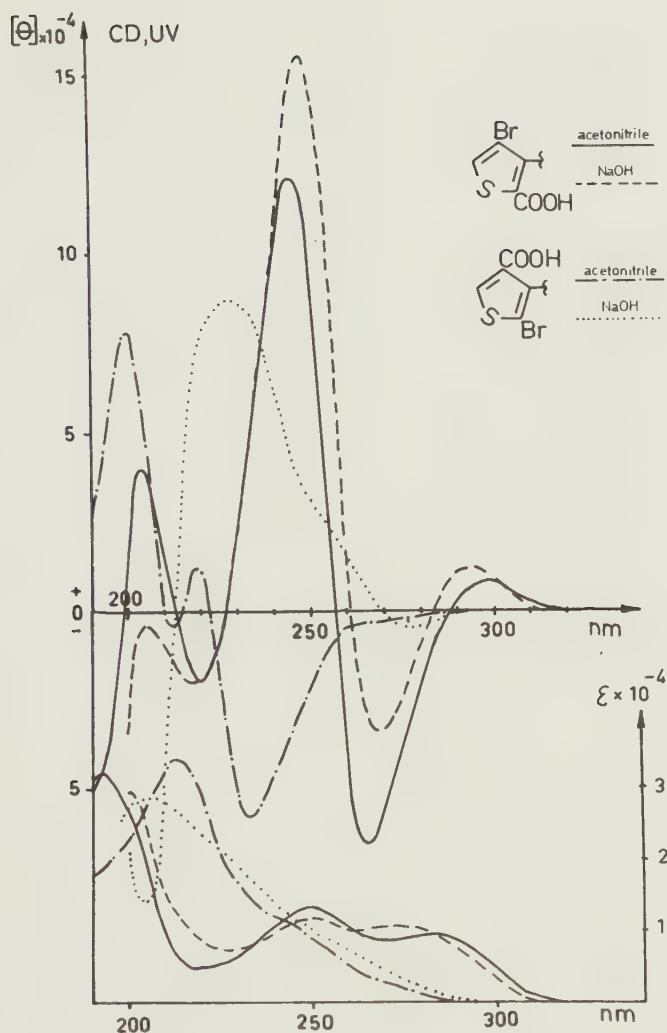


Figure 2. UV and CD spectra of (R)-(+)-4,4'-dibromo-2,2'-dicarboxy-3,3'-bithienyl in acetonitrile (—) and in 0.01 N sodium hydroxide (---) and of (R)-(-)-2,2'-dibromo-4,4'-dicarboxy-3,3'-bithienyl in acetonitrile (-·-) and in 0.01 N sodium hydroxide (···).

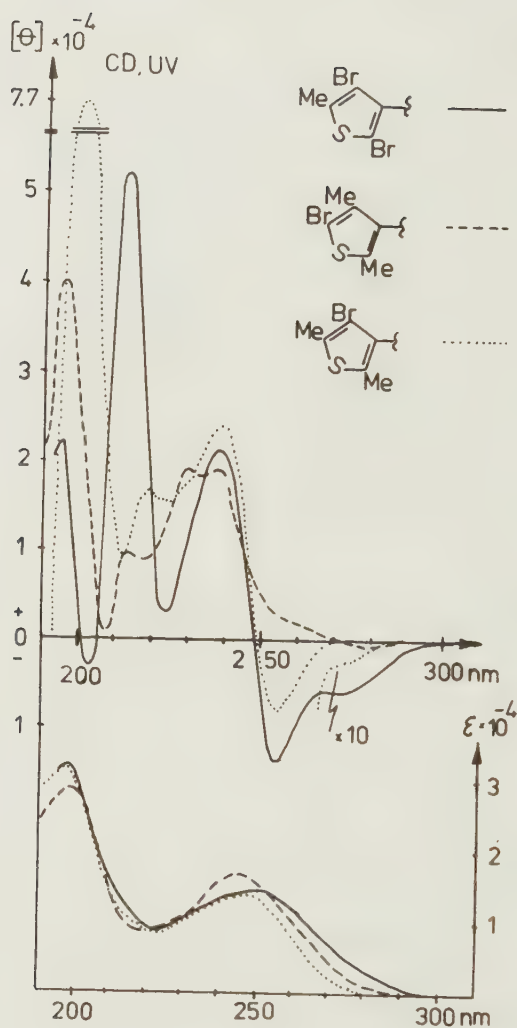


Figure 3. UV and CD spectra of (R)-(-)-2,2',4,4'-tetrabromo-5,5'-dimethyl-3,3'-bithienyl (—), (R)-(-)-5,5'-dibromo-2,2',4,4'-tetramethyl-3,3'-bithienyl (---) and (R)-(+)-4,4'-dibromo-2,2',5,5'-tetramethyl-3,3'-bithienyl (...) in cyclohexane.

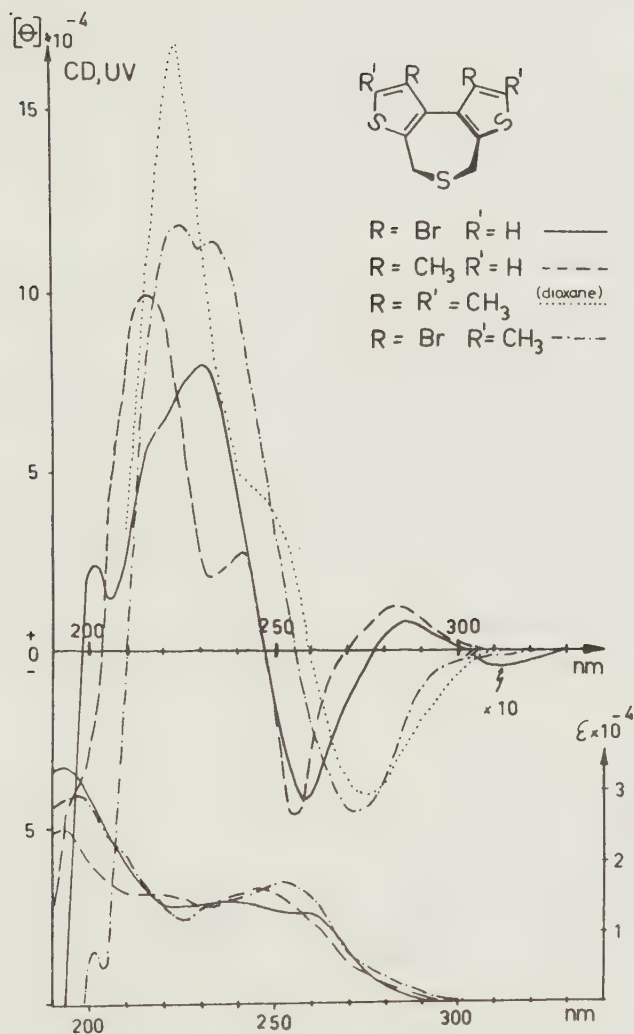


Figure 4. UV and CD spectra of (R)-(-)-1,9-dibromo-4,6-dihydro-dithieno[2,3-c:3',2'-e]thiopyran (—), (R)-(+)-1,9-dimethyl-4,6-dihydro-dithieno[2,3-c:3',2'-e]thiopyran (---), and (R)-(-)-1,9-dibromo-2,8-dimethyl-4,6-dihydro-dithieno[2,3-c:3',2'-e]thiopyran (-.-) in cyclohexane and CD spectrum of (R)-1,2,8,9-tetramethyl-4,6-dihydro-dithieno[2,3-c:3',2'-e]thiopyran in dioxane.

Methyl groups, and especially bromines, at the 5,5'-positions may reduce the negative portion of the curve above 250 nm (Fig. 3), probably in part due to enhancement in intensity of an overlapping positive band at longer wavelengths (9, 12, 14). Bromomethyl groups at the 4,4'-positions appear to have a similar effect (14).

3,3'-Bithienyl-4,4'-dicarboxylic acids and 3,3'-bithienyl-4-monocarboxylic acids of (R)-configuration in neutral solvents seem to be characterized by a negative effect near 240 nm (13, 14, 15) (Fig. 2). The spectra of the corresponding disalts exhibit several positive bands at medium and longer wavelengths, including the 240 nm band (13, 14) (Fig. 2). The spectra of the 4,4'-dicarboxylic acids thereby deviate from those of most bithienyls. The negative 240 nm band (neutral solutions) is observed in the spectra of 3,3'-bithienyl-4,4'-dicarboxylic acids with various 2,2'-substituents such as bromines and methyl, nitro and formyl groups, which may provide a relatively safe basis for configurational assignments of compounds of this type. The spectra of the dimethyl esters may be similar to those of the corresponding carboxylic acids (13, 14); however, that of the ester of IX is different.³¹

7.2 Conformations from CD spectra

The conformation of most 3,3'-bithienyls appears to be cis-skew as determined from the CD spectra, but safer conclusions may be drawn after the completion of current work on a bridged optically active 3,3'-bithienyl of trans-skew conformation. As mentioned just above the characteristic CD pattern observed in the spectra of most 3,3'-bithienyls is exhibited by bridged compounds of type XXXI (Fig. 4). These necessarily have a cis-skew conformation, and provided that this is reflected in the signs of the 250 nm CD effects it follows that the conformation of all 3,3'-bithienyls of (R)-configuration, which exhibit a similar pattern, should also be cis-skew. In the case of the dimethyl ester of 2,2'-dicarboxylic acid XVII X-ray analysis⁵⁷ and CD investigations on crystals⁵⁸ have indicated that the type of spectra exhibited by this class of

compounds in solutions may be consistent with a cis-skew conformation (14).

Preliminary results from X-ray analyses⁵⁷ and solid state CD⁵⁸ indicate that the 4,4'-dicarboxylic acids, which are characterized by a negative 240 nm effect, may also be present in a cis-skew conformation in for example acetonitrile (13, 14). In the case of VII a large separation of the pK_a values permitted the study of the CD spectrum of the corresponding acid salt (13). This spectrum is nearly the mirror image of that of the diacidic form of VII, but the monoanion probably has a cis-skew conformation as well due to internal hydrogen bonds. Thus, the reversal of the spectrum on ionization to monoanion or dianion, which at first was considered to depend on a change in the helicity of the biaryl skeleton, may be caused by conformational and other changes in the carboxylic groups at the 4,4'-positions (13, 14). Probably, the negative ("wrong") sign observed by Mislow et al. in the spectrum of (R)-IV (Section 1.1) and the negative signs of the 240 nm bands of the (R)-3,3'-bithienyl-4,4'-dicarboxylic acids and their dimethyl esters (13, 14) (and of the dimethyl ester (13) of the open diphenic acid (R)-XII) have similar origins.

It is well known that CD spectra provide only one piece of information at a time with respect to geometry; absolute conformations can only be deduced in the case of conformationally rigid molecules without mobile substituents, and the conformations of, in the present case, both the biaryl skeleton and flexible substituents cannot be determined, even if the absolute configuration is known. Conformations are discussed in the following sections as well.

7.3 Comparisons with CD spectra of biphenyls and biselenienyls

In Paper (12) the spectra of 2,2'- and 4,4'-bridged dithienothiepins of type XXXI with bromines or methyl groups as substituents are compared with those of biphenyls XXXII and XXXIII. In these compounds no flexible substituents are present. (Methyl groups are considered as "extended atoms".⁴⁹) Both the absolute configurations and the conformations are known

(helicity (M_x) for the (R)-biaryls). The CD spectra of these compounds with related absolute geometries are very similar.

The resemblances of the spectra of the bridged bithienyls and biphenyls strongly indicate that the two biaryl systems are also electronically closely related (12). It appears to be possible to point out corresponding CD bands in the bithienyl and biphenyl spectra.

The analogous conclusion was reached on comparing the spectra of some 3,3'-bithienyl-4,4'-dicarboxylic acids (VII, XIV, XVIII and the 5,5'-dibromo derivative of the latter) with those of diphenic acids XII, XXVII and XXVIII (13, 14), and with those of biselenienyl XXVI (13). Corresponding Cotton effects could be identified in the spectra of the members of all three biaryl systems (13).

Of great value in this connection were the monoanions of compounds VII, XII and XXVI, which exhibit well separated pK_a values, indicating internal hydrogen bonds in the monoanions (13). Thereby not only are the conformations fixed to cis-skew, but also the natures and relative twists of the carboxylic groups are made equivalent in the three different compounds. Probably as a consequence of this the CD spectra of the species with the same absolute configurations are very similar although the spectra of the diacidic and dianionic forms in particular display great differences (13). Thus the sodium hydroxide solution spectrum of (R)-XII is the mirror image of that of (R)-VII (13). The same is true for the spectrum of the 5,5'-dibromo derivative of (R)-XVIII compared to that of (R)-XXVIII in acetonitrile (14). This might be explained if it were assumed that the compounds of the same configurations have different conformations, which means opposite helicities. However, there are indications that in the cases mentioned the conformation might be cis-skew, i.e. (M_x)-helicity for the (R)-biaryls and (P_x)-helicity for the (S)-biaryls. Therefore it appears that the shapes of the CD spectra may be strongly influenced by flexible substituents.

Unfortunately the CD spectra of the lactons of type XXIX and corresponding 4,4'-bridged compounds cannot be studied. In these molecules the conformation of the ester group is known. However, this is in part compensated by the assumed

intramolecular hydrogen bonds in the monoanion of VII (13).

In 3,3'-bithienyl the ortho positions are not identical as they are in biphenyl. The 4,4'-positions of 3,3'-bithienyl appear to be more comparable than the 2,2'-positions to the ortho positions of biphenyl (13, 14). The CD spectra of the 4,4'-dicarboxylic acids are more similar than those of the 2,2'-dicarboxylic acids to the spectra of the diphenic acids in various respects (13, 14). The relations of positions mentioned above is also indicated from comparisons of the spectra of nitro compounds I, IX and X; those of I and IX are similar at shorter wavelengths, whereas at longer wavelengths, where the spectra probably are dominated by effects determined by the nitro groups, the CD spectra of I and X are similar (13).

In the biselenienyl series only a few compounds are available. The CD spectra of the 4,4'-bis(hydroxymethyl) derivatives of VII and XXVI are similar.³⁵ That of the biselenienyl is shifted 10-15 nm towards longer wavelengths relative to the spectrum of the bithienyl.

The spectrum of XXVI in neutral solvents is similar to those of the 3,3'-bithienyl-2,2'-dicarboxylic acids, but the corresponding dianion exhibits a CD curve which resembles those of the 4,4'-dicarboxylic acids and the diphenic acids in basic solvents (13).

From the above it may have been clear that great care should be taken in drawing conclusions of stereochemical relationships from comparisons of the CD spectra of members of different biaryl systems. This may be possible only if the geometries in part can be deduced or postulated on the basis of other evidence (bridging, internal hydrogen bonds). It was empirically found that for example the configurations of open 3,3'-bithienyl-2,2'-dicarboxylic acids were reflected in their CD spectra. This probably depends on a similar conformation and a similar twist of the carboxylic groups in these related compounds, which cannot be presumed on comparing members belonging to different biaryl systems even if they are substituted in a analogous way.

7.4 Analysis of CD spectra

Some CD spectra have been analysed in detail with the intention of identifying corresponding bands in the spectra of various types of compounds (9, 12, 13). This may be of interest from many points of view. A greater understanding of the compositions of the biaryl spectra may be valuable for obtaining stereochemical information. Thus, similarities between spectra of compounds of related stereochemistry with respect to the presence and signs of bands could be pointed out in some cases despite great apparent differences in curve shapes (e.g. of 2,2'- and 4,4'-bis(bromomethyl) compounds (14)).

To evaluate the mechanism of optical activity in a variety of systems a closer identification of the CD bands is necessary. Spectroscopists are interested in the electronic transitions, which are more easily revealed in the CD spectra than in the isotropic absorption spectra, due to the alternating signs of the corresponding bands in the former spectra.

For a future association of the various CD bands with particular electronic transitions, it is necessary to obtain detailed knowledge about the occurrence of these bands in the spectra of different types of compounds and the influence of many factors on the intensities and positions. The great number of CD effects makes this a difficult task and several solutions are possible for the resolution of such complicated spectra as those of biaryls. However, in the author's opinion the risk of drawing incorrect conclusions should not be discouraging in making an attempt to analyse the CD spectra in greater detail; a method of trial and error might be fruitful in the end.

An attempt was made to find a set of partial CD bands, which could explain the shape of the spectra of several related 3,3'-bithienyls. The parameters characteristic for each partial band were estimated and varied, and the partial curves added by the aid of a desk calculator, provided with a plotter, to compare the theoretical curve with the particular experimental one (9, 12). It was found that the long wavelength

parts of the spectra of 2,2'- and 5,5'-dicarboxylic acids and of bromo- and methyl-substituted compounds were probably all similarly composed of 4-5 bands. Valuable information about the compositions of the various spectra over the whole wavelength region was obtained (9, 12). A greater understanding of the influences on the observed spectra of small variations in intensities and positions of the different bands was acquired by the work with the calculator, and thereby relationships of various curves could more easily be deduced.

Additional work with the CD spectra of the 4,4'-dicarboxylic acids might also increase our understanding of this type of curves. These spectra are probably complicated by strong overlapping of bands, indicated from the UV spectra, and the consequence of this on the shapes of the CD curves might be deduced from calculated spectra.

In the case of 2,2'- and 5,5'-dicarboxylic acids, and derivatives of the former compounds, a special Cotton effect arising from the carboxylic groups could not be identified although the intensities of the medium wavelength bands might be influenced of the 2,2'-carboxyl groups.

The CD band associated with the $n \rightarrow \pi^*$ transition of the carboxyl group is found at 210-215 nm in saturated aliphatic compounds.⁵⁶ However, in the case of the spectra of dialdehyde compound XXIII and its dimethyl ester a relatively weak CD band exhibiting fine structure was observed at about 350 nm (15). This Cotton effect is most probably associated with the $n \rightarrow \pi^*$ transition of the formyl chromophore, and it is situated in a region where it is observed in the CD spectra of α, β -unsaturated carbonyl compounds.^{24, 56} In analogy with this the CD effect associated with the $n \rightarrow \pi^*$ transition of the carboxyl group in the present case should be sought in the region where it is observed in the spectra of α, β -unsaturated carboxylic acids, i.e. at about 250 nm.⁵⁶ In this region intense CD effects originating from aromatic transitions are situated, which probably overlap effects from the carboxylic transitions. It cannot be excluded that the "unexpected" negative sign in the spectra of the 4,4'-dicarboxylic acids or the special shapes of the curves of VII and XIV in this region (13, 14) might at least partly originate from transitions in the carboxyl groups in

analogy with previous suggestions by Mislow et al. in the case of IV (Section 1.1). However, evidently several CD bands are influenced by the carboxylic groups at the 4,4'-positions of 3,3'-bithienyl, and most probably these groups merely perturb the aromatic transitions in a special way in certain conformations relative to the aromatic rings. For example, from Fig. 1 of Paper (1) it may be clear that by rotation around the various bonds within a carboxylic group parts of this group may be situated in other sectors than those occupied by less flexible substituents. The perturbation of these parts may have a similar effect on the CD spectrum as a change of the helicity of the biaryl skeleton. Asymmetric solvation may also be of importance.

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